REMARKS.

Claims 1-15 remain in the case. Favorable reconsideration is requested.

Claims 5-7 and 9-14 have been amended herein. The claims as amended enjoy explicit support in the claims as originally filed and in the specification at page 3, first full paragraph. No new matter is added.

The follow remarks address the issues presented in the Office Action in the order of their appearance:

Objection to Claims Reciting Amino Acid Sequences:

This objection has been addressed by amending Claims 11, 12, and 14 to recite the appropriate sequence identification numbers. Withdrawal of the objection is respectfully requested.

Rejection of Claims 1, 8, 10, and 13 Under 35 USC §112, Second Paragraph:

This rejection is respectfully traversed.

As applied to Claim 1, Applicant notes that the Office Action does not specifically point out any deficiency in Claim 1. Because the Office has not pointed out any specific aspect of Claim 1 that fails to comply with the requirements of §112, second paragraph, Applicant respectfully submits that this rejection is improper as applied to Claim 1.

As applied to Claim 8, regarding the term "about two standard deviations above that of the control standard," Applicant directs the Examiner's attention to FIGS. 1 and 2 of the application as filed, their respective legends, and the description of the Examples, beginning at the top of page 4 of the specification. Specifically, note that the graph of FIG. 1 presents the optical density (O.D.) of an ELISA test according to the present invention for several groups of human patients:

(C) = healthy control group;

(AS) = patients with ankylosing spondylitis;

(RA) = patients with rheumatoid arthritis;

(CVA) = patients with cerebro-vascular accidents;

(ENC) = patients with viral encephalitis;

(MS) = patients with multiple sclerosis;

(CJD) = patients with Creutzfeldt-Jakob disease.

Beginning at the top of page 4, the specification contains a clear description of the ELISA used to generate the data presented in FIG. 1. The ELISA format, of course, is an exceedingly well-known and very sensitive colorimetric assay format. See, for example, Exhibit A, attached hereto, which is an excerpt from "Current Protocols in Molecular Biology," vol. 2, © 1998, describing several different types of ELISAs.

As noted at page 5, lines 6 and 7 of the specification, the ELISA data presented in FIGS. 1 and 2 of the application were generated using a micro-ELISA plate reader at a wavelength of 630 nm.

Thus, in the exact same fashion as presented in FIG. 1, a population of healthy individuals is tested according to the present method and the resulting data points are tabulated to generate a population standard deviation for the collection of healthy individuals tested. Generating a standard deviation from a set of data points is a very basic mathematical operation that is taught in every introductory statistics text book. The standard deviation is a measure of how dispersed a set of data points are about the mean for all of the points. Thus, if the data points are very closely clustered about the mean, the standard deviation is small; if the data points are widely scattered about the mean, the standard deviation is large.

Specifically, the standard deviation is the square root of the variance, or, mathematically speaking:

standard deviation = $\{\sigma^2 = \Sigma(x-\mu)^2/N\}^{1/2}$

where x represents the value of each data point, μ is the mean of the data points, and N is the number of data points. Therefore, to generate a standard deviation for a population of data points, first the mean (*i.e.*, the average) value is generated. This is "μ." The mean, "μ" is subtracted from each data point "x," and the square of the difference is taken. These squares are then added together and the sum is divided by the number of data points in the population. This value is σ^2 (the variance). Taking the square root of the variance gives the standard deviation.

In short, one of skill in the art is perfectly capable of generating a standard deviation for any set of data. Most calculators will do the computation automatically, as will many ELISA plate readers.

Thus, after the population of healthy control individuals are tested, the colorimetric values are tabulated and a standard deviation is generated for the control population using the above-noted equation. A person suspected of suffering from a de-myelinating disease or spongiform encephalopathy is then tested in the same fashion and the colorimetric value for that individual is compared to the mean value for the control population. If the value for the test subject is about two standard deviations higher than the control population, the test is considered positive.

The level of antibodies that indicates a positive result is therefore a level that is at least about 2 standard deviations higher than the level of antibodies found in a control population of healthy individuals, as is clearly illustrated and described in FIG. 1.

Because the specification clearly describes using a healthy control population to generate a standard deviation of the test results, and then comparing the results for a given individual suspected of suffering from a de-myelinating disease or spongiform encephalopathy, Applicant respectfully submits that there is nothing ambiguous or unclear regarding Claim 8. Applicant therefore further submits that as applied to Claim 8, this rejection is clearly improper. Withdrawal of the rejection is requested.

Regarding Claims 10 and 13, this rejection is believed to have been obviated by appropriate amendment to the claims. Specifically, Claim 10 has been amended to recite that the peptide sequence in question has "sufficient conformational similarity to an *Acinetobacter* epitope such that the antibodies tested for are cross-reactive with the Acinetobacter epitope." In a similar fashion, Claim 13 has been amended to recite that the peptide sequence in question "is conformationally sufficiently similar to an *Acinetobacter* epitope to bind to antibodies that bind to the *Acinetobacter* epitope." These passages are explicitly supported in the first full paragraph found at page 3 of the specification, where it is noted that:

> Peptide sequences may be used which have minor variations in amino-acid sequence from the above-mentioned epitopes or prepared peptides but are conformationally sufficiently similar to them that they also bind to the relevant antibodies.

These changes to Claims 10 and 13 are believed to render moot this aspect of the rejection.

Regarding the words "conformational" and "conformationally" as used in Claims 10 and 13 respectively, these words are derived from the common meaning of the root word "conformation" as used in chemistry, to wit:

> **Conformation** [ORG CHEM] In a molecule, a specific orientation of the atoms that varies from other possible orientations by rotation or rotations about single bonds; generally in mobile equilibrium with other conformations of the same structure.

See Exhibit B, attached hereto, which is the corresponding dictionary entry for "conformation" from the McGraw-Hill *Dictionary of Scientific and Technical Terms*.

In light of the above comments and amendment to the claims, Applicant respectfully submits that the rejection of Claims 1, 8, 10, and 13 under 35 USC §112, second paragraph is no longer tenable. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 1-15 Under §103(a) Over Prusiner et al. and Hartnett et al. in View of Marchalonis et al.:

Applicant respectfully traverses this rejection because the **combined** references do not teach or suggest any link whatsoever between elevated levels of anti-Acinetobacter IgA antibodies and the presence of de-myelinating or spongiform disease in the subject tested.

Specifically, the primary reference to Prusiner et al. fails entirely even to mention a single microorganism from the genus Acinetobacter. The Prusiner et al. reference also fails entirely to mention any link between elevated levels of anti-Acinetobacter IgA antibodies and de-myelinating or spongiform disease.

In fact, this reference explicitly teaches away from the present invention, wherein a bacteria of the genus Acinetobacter has been found to be linked to de-myelinating and spongiform diseases. Stanley Prusiner, the 1997 Nobel Prize winner in Medicine, is known worldwide as the founder and foremost proponent of the prion theory to explain the etiology and transmission of spongiform encephalopathies. The Prusiner et al. patent

cited in support of this rejection clearly teaches that these types of diseases are caused not by bacteria, but by prions—highly stable infectious proteins. Thus, the Prusiner et al. patent neither teaches, nor makes any suggestion that spongiform diseases or de-myelinating diseases are caused by any type of microorganism or even related to any type of microorganism. The Prusiner et al. patent simply fails entirely to make any such connection whatsoever.

Combining the Prusiner et al. patent with both the Hartnett et al. and the Marchalonis et al. references does not cure the fatal flaw in the primary reference because neither of these two references teach such a connection. The **combined** teaching of Prusiner et al., Hartnett et al. and Marchalonis et al. does not teach or suggest any link between elevated levels of anti-Acinetobacter IgA antibodies and spongiform diseases or de-myelinating diseases. The only teaching of such a connection is supplied in Applicant's own disclosure. However, it is well settled law that Applicant's own disclosure cannot be used to supply the motivation or suggestion that is lacking in a combination of prior art references.

Specifically addressing the secondary references, the Hartnett et al. paper is concerned solely with a description of the genes required to express protocatechuate-3,4-dioxygenase in *Acinetobacter calcoaceticus*. This reference, however, is completely silent with regard to any causative or predictive link between spongiform diseases or de-myelinating diseases and antibodies to Acinetobacter species.

The Marchalonis document is nothing more than the table of contents from an introductory immunochemistry textbook. This reference is also wholly silent regarding any link between spongiform diseases or de-myelinating diseases and antibodies to Acinetobacter species or antigens derived therefrom.

Thus, the **combined** references, *i.e.*, the entire teaching of all of the Prusiner et al., Hartnett et al. and Marchalonis et al. references, nowhere teaches or suggests the predictive link between anti-Acinetobacter antibodies and spongiform and de-myelinating diseases. Thus, the combined references do not render obvious any of Claims 1-15.

Applicant further notes that there is no motivation for combining these three references in the first instance, minus an improper use of Applicant's own disclosure. The Prusiner et al. patent deals solely with prions. It is completely silent with regard to

bacteria of the genus Acinetobacter. Vice-versa, the Hartnett et al. reference is totally unrelated to prions, says absolutely nothing about spongiform or de-myelinating diseases, and does not have any apparent application in the treatment of any disease state in mammals. The Marchalonis et al. document is a standard textbook. There is no motivation contained **within the applied references themselves** to make the combination in the first place.

Applicant therefore respectfully submits that the Office has not established a *prima facie* case of obviousness with respect to Claims 1-15 because: 1) there is no motivation to combine the claims in the first place; and 2) even if the references are combined, the combination fails entirely to teach or suggest the invention claimed.

Applicant thus submits that the rejection of Claims 1-15 under §103(a) in view of Prusiner et al., Hartnett et al. and Marchalonis et al. is improper. Withdrawal of the rejection is requested.

CONCLUSION

Applicant submits that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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Certificate of Mailing: I hereby certify that this Response and the papers indicated as being transmitted herewith is being deposited with the United States Postal service on this date 7 May 2002, in an envelope as "Express Mail Post Office to Addressee, Mailing Label No. EL847502395US addressed to the Assistant Commissioner for Patents, Washington, DC 20231.

Marcia A. Layton 7 May 2002
Marcia A. Layton date

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

SERIAL NO: 09/646,579 ART UNIT: 1645

FILING DATE: 12/27/2000 EXAMINER: Fields, I.

INVENTOR: Ebringer

TITLE: **Diagnosis of Spongiform or De-Myelinating Disease**

MARKED UP PARAGRAPHS, 37 CFR §1.121(b)(1)(iii)

At page 3, please delete the paragraph at lines 3-11, and insert in its place the following paragraph:

-- In carrying out the present invention, the test is for antibodies which bind to an epitope present in or derived from the *Acinetobacter* species. The antigen used in the test may be the whole organism or at least one prepared peptide sequence corresponding to an *Acinetobacter* epitope. Alternatively, peptide sequences may be used which have minor variations in amino-acid sequence from the above-mentioned epitopes or prepared peptides but are conformationally sufficiently similar to them that they also bind to the relevant antibodies. For example, peptides having the sequence RFSAWGAE **(SEQ. ID. NO: 1)** or ISRFAWGEV **(SEQ. ID. NO: 2)** may be used. --

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TITLE: **Diagnosis of Spongiform ~~or De~~-Myelinating Disease**

MARKED UP CLAIMS, 37 CFR §1.121(c)(1)(ii)

1. A method for detecting a de-myelinating disease or spongiform encephalopathy in mammals which comprises testing a biological sample obtained from the mammal for IgA antibodies which bind to an *Acinetobacter* antigen.

2. A method according to claim 1, in which the *Acinetobacter* is one which presents to the mammal an antigen which exhibits molecular mimicry with the myelin of the mammal.

3. A method according to claim 1, in which the antibodies are indicative of prior infection by *Acinetobácter calcoaceticus.*

4. A method according to claim 1, in which the antibodies tested for are antibodies which bind to an epitope present in or derived from the *Acinetobacter* species or to a prepared peptide sequence corresponding thereto.

5. **[AMENDED]** A method according to **[any of claims]** **claim** 1, in which the disease tested for is bovine spongiform encephalopathy.

6. **[AMENDED]** A method according to **[any of claims]** **claim** 1, in which the disease tested for is multiple sclerosis in humans.

7. **[AMENDED]** A method according to **[any of claims]** **claim** 1, in which the disease tested for is Creutzfeldt-Jacob disease in humans.

8. A method according to claim 1, in which antibodies are assayed and a positive result is indicated by levels of antibodies at least about two standard deviations above that of control samples.

9. **[AMENDED]** A test kit for use with a method according to **[any of claims]** **claim** 1, in which the test antigen is the whole *Acinetobacter* organism or at least one prepared peptide sequence corresponding to an *Acinetobacter* epitope, said test kit including a secondary antibody against the human, bovine, or other mammalian IgA.

10. **[AMENDED]** A method according to claim 1, in which the antibodies tested for are antibodies which bind to a peptide sequence [conformationally similar] **that has sufficient conformational similarity** to an *Acinetobacter* epitope **such that the antibodies tested for are cross-reactive with the Acinetobacter epitope**.

11. **[AMENDED]** A method according to claim 10, in which the epitope is the peptide sequence ISRFAWGEV **(SEQ. ID. NO: 2)**.

12. **[AMENDED]** A method according to claim 10, in which the epitope contains the peptide sequence RFSAWGAE **(SEQ. ID. NO: 1)**.

13. [**AMENDED**] A test kit for use with a method according to claim 10, in which the test antigen is a peptide sequence which is conformationally sufficiently similar to an *Acinetobacter* epitope to bind to [the relevant] antibodies **that bind to the *Acinetobacter* epitope**, said test kit including a secondary antibody against **[the]** human, bovine, or other mammalian IgA.

14. **[AMENDED]** A test kit according to claim 13, comprising a peptide having the sequence RFSAWGAE **(SEQ. ID. NO: 1)** or ISRFAWGEV **(SEQ. ID. NO: 2)**.

15. A test kit according to claim 9, in which the secondary antibody is a rabbit anti-human IgA or rabbit anti-bovine IgA.